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A Biologically Inspired and Protein-Based Bio-Cyber Interface for the Internet of Bio-Nano Things

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ABSTRACT

The Internet of Things (IoT) has changed the way how we interact with our physical environment, enabling connectivity and communication between physical and virtual entities, e.g., for digital twin applications. However, as we step beyond the IoT, developing the Internet of Bio-Nano Things (IoBNT), where biological and nanoscale entities will be included in our communication networks, includes challenges as well as opportunities. In the IoBNT, the role of Bio-Cyber Interfaces (BCIs) is still underscored, representing necessary building blocks that ensure the bidirectional information exchange between biological and digital communication systems. The application area of the IoBNT spans diverse domains, e.g., healthcare, personalized medicine, or environmental monitoring. This work proposes a theoretical framework for a BCI, leveraging advances in biotechnology, nanotechnology, and communication engineering to establish an interface for exchanging information between biological entities, nanoscale devices, and the digital world. Therefore, we discuss the key components of the proposed BCI framework. Furthermore, we survey the existing literature of biologically inspired BCIs and outline potential use cases and benefits of integrating BCIs in the IoBNT for various domains, such as healthcare and environmental monitoring.

1. Introduction

In recent years, scientific progress in biotechnology and nanotechnology has led to new approaches and interdisciplinary collaborations in electrical and communication engineering, giving rise to the concept of the Internet of Bio-Nano Things (IoBNT) (Akyildiz et al., 2015) including a new communication paradigm called Molecular Communication (MC). MC is inspired by entities of our living environment, such as cells or organisms, and involves exchanging information through chemical signals. This process includes the transmission, propagation, and reception of chemical signals in the presence of molecules, hormones, or nanoparticles, unlike the use of electromagnetic waves in conventional ElectroMagnetic Communication (EMC) (Nakano et al., 2013). Research in MC mainly focuses on synthetic MC, which is inspired by natural MC, i.e., naturally occurring chemical communication (Nakano et al., 2013; Lotter et al., 2023). Synthetic MC is based on establishing synthetic communication links through chemical communication, passing the way towards the IoBNT. The IoBNT describes an inhomogeneous communication network of nanoscale devices, biological entities, and cyber–physical entities (Akyildiz et al., 2015). It facilitates communication among nanoscale and biological components, unlocking applications across various domains. In healthcare, synthetic MC can revolutionize targeted drug delivery (Chude-Okonkwo et al., 2017; Nakano et al., 2012). Nanoscale devices or nanorobots communicate with biological systems, releasing drugs within the human body. In environmental monitoring (Nakano et al., 2012), nanosensors communicate with each other, collecting data on, e.g., pollution levels. Furthermore, the IoBNT has the potential to transform synthetic biology by enabling communication among synthetic cells or nanorobots (Farsad et al., 2016; Nakano et al., 2012).

Additionally, the IoBNT represents a considered frontier in the evolution of future beyond-5G communication networks (Guo et al., 2021; Hofmann et al., 2022). Unlike its predecessors, beyond-5G communication networks harness the capabilities of integrating the living environment into wireless communication networks of the future. Beyond-5G networks shall not only include classical EMC - alternative communication paradigms such as optical, quantum, or MC extend the network of the future (Schwenteck et al., 2023). Therefore, beyond-5G networks hold the potential to revolutionize connectivity, reliability, energy efficiency, and sustainability.

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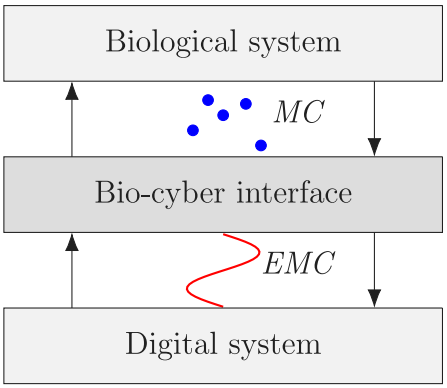

Fig. 1. Graphical scheme of BCIs. The BCI serves as a bidirectional interface between a biological system and a digital system.

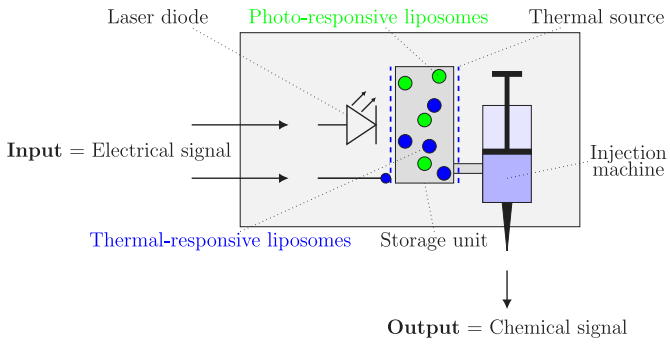

Fig. 2. Scheme of the in Chude-Okonkwo et al. (2016) proposed electro-bio interface including the presented injection machine.
Source: Adapted from Chude-Okonkwo et al. (2016, Fig. 4).

An essential element of the IoBNT is a so-called Bio-Cyber Interface (BCI), which connects biological entities, mainly in the micro- and nanoscale domain, and state-of-the-art cyber–physical systems, enabling communication and interaction. The concept of a BCI involves converting signals, e.g., biochemical signals generated in intra-body nanonetworks to electrical signals utilizable in the digital domain of the cyber–physical world, and *vice versa* (Zafar et al., 2021), enabling a bidirectional information exchange, cf. Fig. 1.

In this work, we aim to provide a new molecular basis for a BCI, based on the energy landscapes (i.e., a multidimensional representation of the potential energy of a system) of a dynamic gearbox (Schulte et al., 2024) in the form of a G Protein-Coupled Receptor (GPCR). GPCRs represent the most extensive category of membrane proteins, orchestrating various cellular reactions triggered by hormones and neurotransmitters. They also play pivotal roles in fundamental sensory processes such as vision, olfaction, and taste perception. Therefore, we briefly review existing BCI devices inspired by biology. In addition, we propose the theoretical architecture and the design of a biological BCI, converting signals from the molecular domain to the optical domain using fluorescence or bioluminescence. Finally, we outline potential applications, discuss ethical, societal, and regulatory considerations, and introduce limitations for our proposed BCI in the IoBNT.

The remainder of this work is structured as follows. Section 2 gives a comprehensive overview of biologically inspired BCIs in the literature. Section 3 describes the principle of GPCRs as BCIs. Our proposed theoretical setup of a BCI, containing a recognition, a transducing, a reporter, and a processing unit, is described in Section 4. Section 5 discusses the limitations and ethical, societal, and regulatory considerations of using BCIs. Finally, Section 6 briefly summarizes the presented work and gives an outlook on future research.

2. Literature review: Biologically inspired BCIs

This section briefly reviews the existing literature for biologically inspired BCIs to give the reader an overview. A summary of biologically inspired BCIs in the literature can be found in Table 1.

BCI	Transduction mechanism
Biologically inspired BCI (Chude-Okonkwo et al., 2016)	**Electrical to biochemical signal:** Photo-responsive and thermal-responsive biomolecules **Biochemical to electrical signal:** Bioluminescence

In 2016, Chude-Okonkwo et al. (2016) presented a model and a possible architecture for a BCI, connecting a digital system to a biological system and *vice versa* in the context of the IoBNT, applicable in a future healthcare delivery scenario. The presented BCI transduces an electrical to a biochemical signal using photo-responsive and thermal-responsive biomolecules and a biochemical signal to an electrical signal using a bioluminescence reaction. A logic gate converts a binary input from the decoder into a thermal (thermal source) or an optical effect (laser diode) for the electro-bio interface. The thermal or optical stimulus releases molecules from a reservoir. Chude-Okonkwo et al. (2016) consider two sets of liposomes as molecules responding to a change in temperature and varying light. For the output of the released molecules into the biological system, Chude-Okonkwo et al. (2016) schematically present an injection machine, cf. Fig. 2. The released molecules, i.e., the biochemical signals, propagate through the human body using the cardiovascular system.

For the bio-electro interface, the BCI detects the presence of information molecules within the blood vessel. Therefore, Chude-Okonkwo et al. (2016) design a "subdermal/transdermal system with receptor-like probes". The sensor part of the bio-electro interface comprises a cellular structure that is synthesized or genetically modified. Nanopores or membrane receptors function as probes into the cardiovascular system. These probes identify information molecules circulating through the vascular system. Depending on the detected molecules, the probe may consist of complementary biochemical molecules (Chude-Okonkwo et al., 2016). The detection process involves ligand–receptor binding, i.e., the moving information molecule interacts with the receptor probe. Alternatively, the information molecules might permeate directly into the cellular structure. This structure can be a bioluminescent reporter triggering the production of a reporter enzyme, e.g., luciferase. The produced luciferase reacts by generation of bioluminescence from the luciferin substrate, which is added to the system. A light sensor in the nanoscale domain detects the emitted light, generating an electrical signal output.

BCI	Transduction mechanism
SiNW FET-based BCI (Kuscu and Akan, 2015, 2016)	**Biochemical to electrical signal:** BioFET

Kuscu and Akan (2015) proposed in 2015 a Silicon NanoWire (SiNW) Field-Effect Transistor (FET)-based biosensor, i.e., a SiNW bioFET, acting as a molecular antenna, converting a biochemical signal into an electrical signal in terahertz band using bioFET technology. BioFETs closely resemble conventional FETs, differing only in an additional biorecognition layer, which can selectively bind the target molecules (Kuscu and Akan, 2016; Poghossian and Schöning, 2014). At the biorecognition layer, tethered receptor molecules, placed on the surface of the FET channel, replace the gate electrode of a conventional FET. The interaction of ligands possessing intrinsic charges with the

Table 1
BCIs inspired by biology, modified from Zafar et al. (2021). 'Exp. setup' and 'Bio.' denote experimental setup and biocompatibility, respectively. 'Two-way' describes the directionality, i.e., down- and uplink capabilities. Biocompatibility refers to the ability of a BCI to perform with an appropriate biological response, i.e., being not harmful or toxic to biological systems (Perrotti et al., 2017).

BCI	Transduction mechanism	Two-way	Exp. setup	Bio.	Scale
Biologically inspired BCI (Chude-Okonkwo et al., 2016)	Electrical ↔ Biochemical	✓	✗	✗ ✓	Macro (electro-bio) Micro (bio-electro)
SiNW FET-based BCI (Kuscu and Akan, 2015, 2016)	Biochemical → Electrical	✗	✗	✓	Micro
Redox-based BCI (Liu et al., 2016; Kang et al., 2018)	Chemical → Electrical	✗	✓	✓	Micro
Signal conversion BCI (Grebenstein et al., 2019)	Optical → Chemical	✗	✓	✓	Micro
FRET-based BCI (Abd El-atty et al., 2020, 2024)	Electromagnetic ↔ Biochemical	✓	✗	✓	Micro
THz-controlled BCI (Elayan et al., 2021b,a, 2022)	Electromagnetic → Biochemical	✗	✗	✓	Micro
Proposed protein-based BCI	Biochemical → Electromagnetic	✗	✗	✓	Micro

surface receptor molecules leads to an accumulation or depletion of the information carriers on the semiconductor's channel. This process modulates the channel's current and conductance, resulting in the outputted current as a function of the concentration of the ligands and the quantity of the ligand charges. BioFETs operate effectively with various pairs of ligands and receptors, such as antibody–antigen and aptamer-natural ligand, making them adaptable for different molecular recognition scenarios (Rogers, 2000). Furthermore, Kuscu and Akan (2015) present a noise model and a deterministic model for SiNW bioFETs used as molecular antennas for the operations of biorecognition and transduction for quantity modulation of the molecules. Quantity modulation describes the concentration adjustment, i.e., encoding the information to be transmitted in the concentration (Kuran et al., 2020). Simulation results in Kuscu and Akan (2015) demonstrate high Signal-to-Noise Ratio (SNR) values at the output of the antenna, i.e., the simulation results justify using SiNW bioFETs as unidirectional BCIs. Kuscu and Akan (2016) expand their work by presenting a model for SiNW FET-based BCIs. Kuscu and Akan (2016) present closed-form expressions, focusing on microfluidic MC, for the SNR at the output of the receiver, the symbol error probability, and for the noise statistics.

BCI	Transduction mechanism
Redox-based BCI (Liu et al., 2016; Kang et al., 2018)	**Chemical to electrical signal:** Redox reaction modality

Liu et al. (2016) proposed a BCI in 2016, transforming a chemical to an electrical signal using the redox modality, i.e., redox reactions. A redox reaction (reduction–oxidation reaction) characterizes a specific class of chemical processes in which electrons are exchanged between two entities. Liu et al. (2016) used electrical stimuli to fabricate the presented dual film coating system, cf. Fig. 3. An outer film recognizes external chemical information in the dual film coating system, i.e., externally released molecules, using a synthetically engineered construct. Subsequently, this recognition triggers the release of an enzyme called β-galactosidase. The enzyme converts a substrate, which is redox-inactive, into a product, which is redox-active. Meanwhile, the inner film, called redox-capacitor film, initiates an oxidative redox-cycling reaction with the redox-active product. The capacitor is discharged by the oxidative redox-cycling reactions, outputting an amplified electrical signal (Liu et al., 2016). Furthermore, Liu et al. (2016) presented measurements verifying the presented BCI functionality. Kang et al. (2018) extended the study in 2018, showing that melanin can serve as an external chemical information carrier. Thereby, melanin from *Sepia* (cuttlefish) commonly models natural melanin. To shuttle electrons from or to melanin, redox mediators, e.g., ABTS (2,2'-azino-bis 3-ethyl-benzothiazoline-6-sulphonic acid), use the redox-cycling reactions.

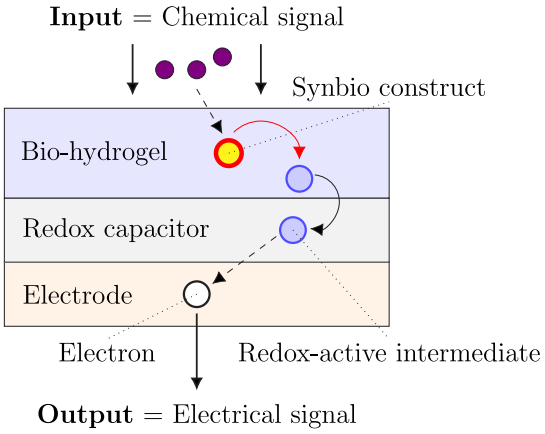

Fig. 3. Proposed hydrogel film (Liu et al., 2016) for converting a chemical signal into an electrical signal.
Source: Adapted from Liu et al. (2016, Scheme 1).

BCI	Transduction mechanism
Signal conversion BCI (Grebenstein et al., 2019)	**Optical to chemical signal:** pH level change due to illumination

In 2019, Grebenstein et al. (2019) proposed a biological interface, converting optical to chemical signals, cf. Fig. 4. The proposed BCI transduces an optical signal, i.e., light, emitted by a diode, into a change of the pH value, i.e., into a chemical signal. Grebenstein et al. (2019) use *Escherichia coli* (E. coli) to realize the modulator as a microscale entity. Thereby, *E. coli* express gloeorhodopsin from *Gloeobacter violaceus*, a light-driven pump for protons. By proton export into the local environment due to external light stimuli, *E. coli* can change the pH value of their surroundings, cf. Fig. 4. For the demodulation of the transmitted signal from the transduced chemical signal – measured in the presented experimental setup by a pH meter acting as the receiver – Grebenstein et al. (2019) developed estimation and detection methodologies. Using the proposed schemes for estimation and detection, the transduction of an optical signal into a chemical signal was achieved with a bit rate of 1 bit/min (Grebenstein et al., 2019).

BCI	Transduction mechanism
FRET-based BCI (Abd El-atty et al., 2020, 2024)	**Electromagnetic to biochemical signal:** FRET **Biochemical to electromagnetic signal:** FRET

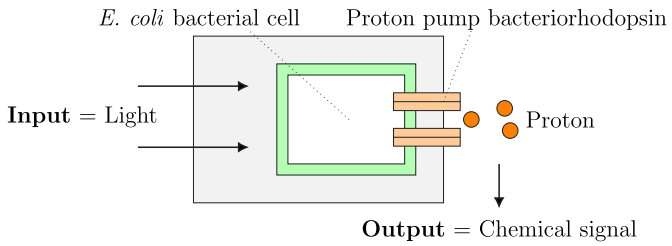

Fig. 4. Schematic model of the in Grebenstein et al. (2019) proposed optical-to-chemical BCI.
Source: Adapted from Grebenstein et al. (2019, Fig. 2).

In 2019, Abd El-atty et al. (2020, 2024) proposed a bidirectional BCI for targeted drug delivery within the framework of the IoBNT using nanomachines. The proposed BCI (Abd El-atty et al., 2020) comprises Förster Resonance Energy Transfer (FRET) and transduces an electromagnetic to a biochemical signal for downlink and a biochemical signal to an electromagnetic signal for uplink. FRET describes a process for transferring energy, which is non-radioactive, in the form of an exciton transfer, occurring between molecular dipole pairs such as donor fluorophore and acceptor fluorophore (Lotter et al., 2023). After finishing the energy transfer, the acceptor reaches an excited state and emits an optical signal (fluorescence). For efficient energy transfer, the pairs have to be in close proximity and in a suitable orientation to each other (Thomas et al., 1978). When a donor fluorophore molecule is exposed to visible light, i.e., due to a light source, the molecules release a photon that can be transferred to the acceptor fluorophore, forming a donor–acceptor FRET pair. For transducing an electromagnetic signal into a biochemical (downlink) signal, the BCI decodes a received external electrical signal and outputs an optical signal. The sent optical signal stimulates a nanotransmitter, i.e., activates a nanotransmitter, in the nanonetwork. Enabled by FRET, exciton information is transmitted through the nanonetwork. The nanonetwork consists of several nanorelays and nanoreceivers. In the proposed scenario (Abd El-atty et al., 2020), the drug molecules are represented by the exciton information. Transducing a biochemical signal into an electromagnetic signal (uplink) is used for monitoring and detecting the treatment of diseased cells in the drug delivery framework (Abd El-atty et al., 2020). To monitor the activation of a nanomachine, the donor and the acceptor can be linked to the protein in an intra-molecular binding, allowing direct import of structural rearrangements within the nanomachine. Depending on the acceptor and donor, the nanomachine can be used as a Bioluminescence Resonance Energy Transfer (BRET) or FRET sensor. However, the donor's energy comes from a chemical reaction — it is not externally excited. In the chemical reaction, a luciferase molecule oxidizes due to the presence of luciferin. The chemical reaction generates energy. Thereby, the emitted photons can be caught by a nearby donor. In the proposed scenario (Abd El-atty et al., 2020), an analyte, e.g., a drug molecule, binds a receptor. Meanwhile, the analyte molecules can enter the bioluminescent bioreporter. Inside the bioreporter, luciferin is converted into oxyluciferin by the enzyme luciferase — light is emitted, i.e., an optical signal.

BCI	Transduction mechanism
THz-controlled BCI (Elayan et al., 2021b,a, 2022)	**Electromagnetic to biochemical/ biomechanical signal:** Biochemical/ biomechanical events due to conformational changes caused by THz radiation

Elayan et al. (2021a,b, 2022) presented a BCI consisting of proteins stimulated with terahertz band frequencies (0.1–10 THz). Due to changes in the conformation of the protein, triggered by vibrational nodes using terahertz waves, biomechanical and biochemical events result (Elayan et al., 2021b,a, 2022). The presented system (Elayan et al., 2021a) consists of a transmitter, i.e., a nanoantenna, and a protein-based receiver. Considering the short-range communication distances among nanomachines, the assumption that the nanoantenna is considered as a point dipole holds true (Johari and Jornet, 2018). The nanoantenna interacts with the protein using terahertz waves, specifically targeting vibrational modes to induce conformational change with functional consequences. Consequently, the electromagnetic field induced by the nanoantenna polarizes the protein. Proteins are dipoles, and a dipole undergoes rotation motion in response to the electric field direction (Martinsen and Grimnes, 2014), i.e., if the electric field direction is reversed, it causes a shift in the alignment of the dipole (Elayan et al., 2021a). The conformational change of the proteins due to the changing direction of the electromagnetic field leads to biochemical/biomechanical reactions (Elayan et al., 2021b), e.g., the release of signaling molecules. Furthermore, the presented BCI (Elayan et al., 2022) offers the potential to influence the protein's conformational states by the regulation of the emission of the terahertz waves from the transmitter, inducing folding or binding processes of the protein. Consequently, varying terahertz band frequencies can enable a precise modulation of receptor activation in both temporal and spatial dimensions (Elayan et al., 2022).

3. Principle of GPCRs as BCIs

To exploit a biological system for interfacing with the cyber–physical world, the system must simultaneously be tunable and controllable, as input and output can be well-defined and measurable. Here, we propose to exploit recent understanding in pharmacology, more precisely in GPCR pharmacology, regarding a molecular understanding of how ligand-induced activation (or inactivation) of the pharmacological receptor translates into conformational rearrangements that can be coupled to a biophysical read-out, such as the emission of light or bioluminescence. GPCRs compose the largest gene family in our genome, with about 800 representatives in humans. While the first GPCR was cloned in the mid 1980s (Dixon et al., 1986), we have now reached a level of understanding of receptor structure, dynamics, function, and pharmacology that allows the design of tunable systems. GPCRs are transmembrane proteins that bind molecules such as hormones or neurotransmitters on the extracellular side. These bodily ligands, e.g., adrenalin or dopamine, induce a conformational change in the transmembrane core of their cognate receptors, feeding into transducer coupling on the intracellular side of the cell membrane, cf. Fig. 5.

Transducer activation in response to receptor activation results in biochemical changes intracellularly such as the activation of heterotrimeric G proteins, production of second messengers, and protein phosphorylation that can be interpreted by the cell as a physiological signal leading, for example, to gene transcription, cell division, migration, or differentiation (O'Hayre et al., 2014; Liu et al., 2024). To describe the concept of cellular communication through GPCRs and heterotrimeric G proteins, we use the classical pathway from GPCRs recruiting stimulatory G proteins as transducers to activate the effector called adenylyl cyclase, a transmembrane spanning enzyme (Ramms et al., 2021). This enzyme uses the Adenosine TriPhosphate (ATP) to generate a diffusable second messenger, cyclic Adenosine MonoPhosphate (cAMP). cAMP, in turn, binds the cAMP-dependent Protein Kinase A (PKA), which serves to phosphorylate and activates transcription factors of the cAMP Response Element Binding (CREB) proteins. Upon nuclear translocation, CREB will act on the level of the DeoxyriboNucleic Acid (DNA) to regulate gene transcription and, thereby, the expression of cAMP-regulated genes and protein products, cf. Fig. 7. It should be underlined, however, that the cellular communication pathway from receptor to gene transcription is not particularly relevant to the concept of GPCRs as a BCI, as proposed here. As elaborated below, the BCI is limited to the ligand, the receptor, and in some regard, also the ability of the receptor to engage with a transducer

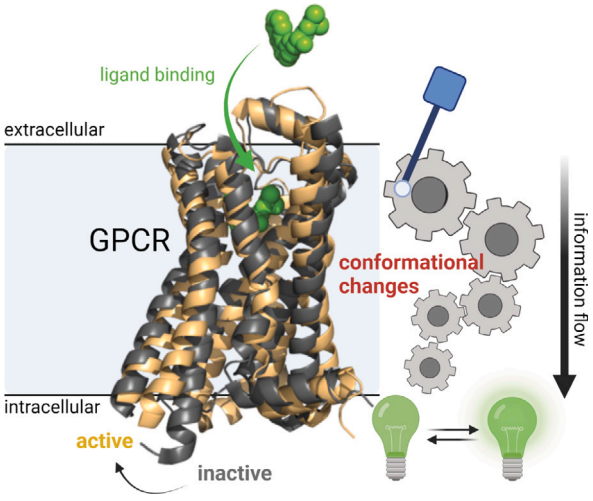

Fig. 5. Scheme for a dynamic gearbox (Schulte et al., 2024) as a BCI. The dynamic gearbox facilitates the conveyance of information from the extracellular environment to the cell's intracellular environment through conformational rearrangements. GPCRs can be connected to a reporting unit, reporting ligand-induced conformational changes as light emission. Schematics were drawn using biorender.com by G. Schulte.

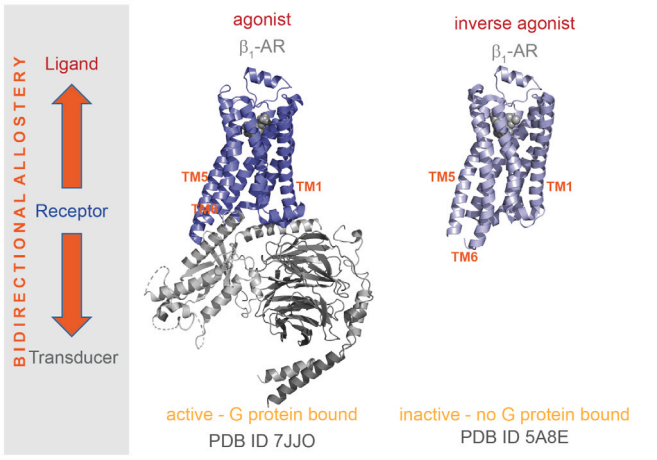

Fig. 6. The bidirectional allostery in the ternary complex model presents the molecular basis for the GPCR-based BCI. The ternary complex model (De Lean et al., 1980) describes the allosteric communication between the agonist binding site within the GPCR and the transducer interaction site on the intracellular side. Agonists with an efficacy equal to 1 activate the receptor to stabilize the functional conformation that can couple to heterotrimeric G proteins. The ligand-induced conformational rearrangements that define G protein coupling build the basis for the BCI. The agonist-bound model presented here for the wild turkey β_1-adrenoreceptor (β_1-AR) is based on the experimental structure with the Protein Database PDB ID 7JJO (Su et al., 2020). Note the opening of the receptor molecule manifesting in a swing out of the TransMembrane domain 6 (TM6) compared to the inactive structure of the same receptor when bound to an inverse agonist. The inactive GPCR (PDB ID 5A8E; Sato et al. (2015)) cannot couple to the heterotrimeric G protein. Receptor proteins are shown in the blue cartoon. The ligands are shown as gray spheres, and the heterotrimeric G protein is shown in gray. The model presentation was created with PyMOL by Schrödinger, Inc. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

such as the heterotrimeric G protein. The concept of allosteric coupling between the ligand, the receptor, and the transducer was initially described in the ternary complex model (De Lean et al., 1980) arguing for a bidirectional transmembraneous allostery through the receptor molecule, cf. Fig. 6. This concept has more recently been refined, allowing not only heterodimeric G proteins as transducers but also different transducer proteins to couple to the receptor, including arrestins, GPCR kinases, and disheveled (Schulte and Wright, 2018; Schulte et al., 2024).

Provided the recent structural biological revolution in the field of transmembrane proteins and GPCRs initiated by the development of new detergents for protein solubilization, cryogenic electron microscopy, as well as a further refinement of receptor ligands and their pharmacology, receptor conformational changes are much better understood in relationship to the receptor's activation status (Ghosh et al., 2015; Safdari et al., 2018). Indeed, receptor conformation can be directly linked to transducer coupling, and ligand activity at the receptor feeds into conformational changes leading to activation, inactivation, and differential transducer coupling (Kenakin, 2016). Thus, the ability to bind a ligand and to elicit a conformational change that either activates (the ligand is an agonist) or inactivates (the ligand is an inverse agonist), the receptor feeds directly into the activation state of the receptor (Latorraca et al., 2016). The ability of a ligand to change the receptor's activity state is referred to as ligand efficacy.

The term efficacy, which describes ligand action at a pharmacological receptor, has evolved from a digital perception with values of 0 and +1 (inactive receptor versus fully active receptor) towards a vectorial measure with values ranging from −1 to 0 and to +1 for a given experimental readout. Initially, receptors were seen as "ON" or "OFF". This oversimplified concept was revisited in parallel with better insight into ligand action at receptors, where, for example, small molecules can act as full agonists (efficacy = 1), partial agonists (efficacy between 0 and 1), antagonists (efficacy = 0), and inverse agonists (efficacy less than 0). As introduced above, the range of efficacy can be explained by intrinsic protein dynamics that reflect a receptor's activation state. These receptor dynamics are relatively well understood for GPCRs. In a physiological context, the spectrum of receptor conformations that can be dynamically probed by the receptor molecule over time is not only dependent on the ligand binding to the receptor and acting to stabilize a specific three-dimensional conformation but also additional factors, such as the lipid bilayer composition, accessory proteins and coupling of intracellular transducer proteins contribute to the complex energy landscapes of receptor conformations available for an individual receptor to probe. An energy landscape is a multidimensional representation of a system's potential energy, where different points on the landscape correspond to different states of the system. The heights of these points indicate the likelihood of those occurring states. In cellular pharmacology, genetically encoded, biophysical, and optical sensors are often used to investigate receptor dynamics and ligand-induced responses in living cells, e.g., in Kozielewicz et al. (2021), Wright and Bouvier (2021), Olsen and English (2022) and Olson et al. (2022). Provided that the most prominent hallmark of the activation of a GPCR is the outward movement of the TM6, which is connected via the IntraCellular Loop 3 (ICL3) with the TransMembrane domain 5 (TM5) of the receptor, the relative position of TM6/ICL3 to the receptor core is monitored in these GPCR biosensors. The biosensors are created by introducing a reporter unit either only in the ICL3 or both in the ICL3 and the C terminal end of the GPCR, depending on employing a fluorescence- or BRET/FRET-based readout, respectively (Haider et al., 2019). Irrespective of the detection method being resonance energy transfer or fluorescence changes, the biosensors report on the ligand-induced structural rearrangements based on the TM6 swing out, cf. Fig. 6. Provided an effective genetically-encoded sensor of receptor conformation is combined with the most ideal receptor ligands acting as a full agonist and inverse agonist, defining ON and OFF, respectively, we could construct a system where ligand input defines the amplitude of a biophysical output (Deupi and Kobilka, 2010), which could implement the basis for a BCI in the IoBNT.

4. GPCR-based BCI setup

The following subsections are based on the presented scheme in Fig. 5 but are also linked to the recognition, transducing, and processing units mentioned in Kuscu and Akan (2016).

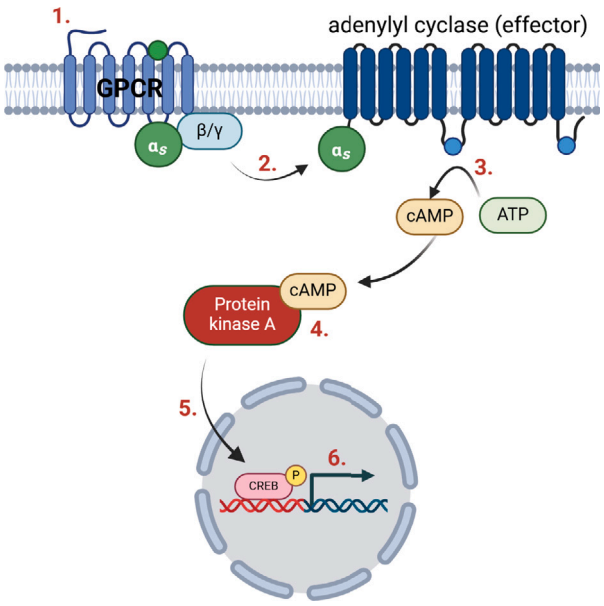

Fig. 7. GPCR signaling as a communication concept. GPCRs communicate by coupling to a variety of intracellular transducers, such as heterotrimeric G proteins. Here, we present GPCR signaling through stimulatory G_s proteins as an example to transduce chemical information from the outside of the cell to the inside, translating chemical information in the form of a soluble hormone such as adrenaline into physiological relevant information manifested as a change in gene expression. The numbers in the scheme depict the chain of events: (1.) An agonist binds and activates the GPCR. (2.) Conformational rearrangements in the receptor lead to G protein coupling and G protein activation. The activated G protein (in this case, the stimulatory G_s protein) acts as a transducer and activates the effector, a transmembrane protein called adenylyl cyclase. (3.) Adenylyl cyclase uses ATP to produce the second messenger cAMP. (4.) cAMP binds and activates cAMP-dependent protein kinase or PKA, which (5.) phosphorylates the transcription factor cAMP-dependent response element-binding protein CREB. (6.) Phosphorylated CREB acts as a transcription factor to regulate gene expression, leading to the expression of CREB-regulated proteins. Schematics were drawn using biorender.com by G. Schulte.

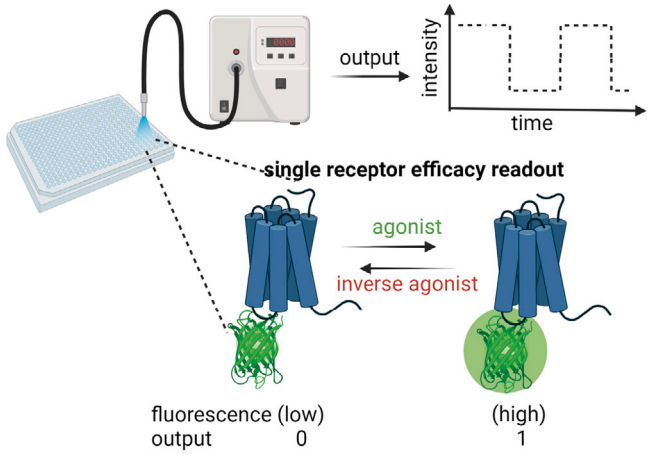

Fig. 8. Scheme of the proposed BCI setup as a directional interface in between MC (can be natural or synthetic) and EMC. Schematics were drawn using biorender.com by G. Schulte.

4.1. Recognition unit — Ligand binding

The ligand binding process can be understood as a recognition unit in the sense of Kuscu and Akan (2016, Fig. 1). The recognition unit serves as the core operational component within molecular sensors, carrying out the crucial task of discerning and identifying specific targets within the designated range of target concentrations. Hormones, neurotransmitters, and small molecule compounds are used as ligands, which are applied with a microfluidic system to a purified sensor in a single receptor preparation. The ligand propagates through the fluid by diffusion and advection. When the ligand binds to the extracellular portion of the GPCR, it induces a conformational change in the receptor according to the efficacy of the ligand.

The proposed GPCR-based BCI can also be adapted to detect different ligands ranging from ions to amino acids to small molecules or peptides and proteins. The ligand-selectivity of the incorporated GPCR defines its selectivity. To some degree, GPCR selectivity can be modified to detect artificial compounds as exemplified by so-called Receptor Activated Solely by a Synthetic Ligand (RASSL)- or Designer Receptor Exclusively Activated by Designer Drugs (DREADD)-based chemogenetic tools (Venkatakrishnan et al., 2014; Urban and Roth, 2015). The cellular sensitivity of GPCRs to their bodily and therapeutically relevant synthetic ligands is usually pico- or nanomolar, defining the sensitivity of the GPCRs in the proposed BCI. Technologically, the sensitivity of a BCI device can be increased by increasing the number of receptors that produce an output signal in relation to the detected ligand. The sensitivity of the BCI system can be optimized predominantly by increasing the transduction yield of the reporter unit (fluorescence output) as well as the sensitivity of the detector as the processing unit.

4.2. Transducing unit — Conformational changes

Ligand binding causes the GPCR to change its shape and become either activated (agonist) or inactivated (inverse agonist), resulting in a conformational change of the receptor protein. The conformational change in the dynamic gearbox (Schulte et al., 2024) enables the coupling to and "activation of heterotrimeric G proteins and other intracellular effectors" (Manglik and Kruse, 2017).

4.3. Reporter unit

In our case, the conformational rearrangement in the receptor protein does not feed into transducer coupling but is instead directly coupled to a biophysical entity (reporter unit) that either reports on a change in BRET, FRET, or in a change in the emission of fluorescence, cf. Fig. 8. Thus, the conformational changes translate directly into the emission of photons. Several of the BRET, FRET, or fluorescence-based GPCR sensors have been described in the literature (Kozielewicz et al., 2021; Haider et al., 2019; Lohse et al., 2012; Patriarchi et al., 2018, 2019; Labouesse et al., 2020).

To design a functional and tunable reporter unit in the form of a single GPCR designed as a BRET sensor or fused to a Circularly permuted Green Fluorescent Protein (cpGFP) moiety, we propose to purify the engineered receptor molecule in detergent micelles and immobilize those on a chip surface. As a variation of this concept and a possibility to stabilize the receptor in the artificial environment, the purified receptor can be embedded in lipid nanodiscs, which exist in many different variations, and the receptor remains functional in a defined lipid environment.

The conformational change and the reporter unit serve, according to Kuscu and Akan (2016), as a transducer. A transducing unit is a component designed to convert one form of energy or physical quantity into another. The primary function of the transducing unit is to transform a measurable physical quantity, such as mechanical, electrical, thermal, or optical signals, into a corresponding output signal. In the case of the GPCR sensors, mechanical force is transformed into photon emission.

4.4. Processing unit — Detection

Finally, a processing unit is a component within an electronic system responsible for executing various computational tasks. The processing unit performs arithmetic and logical operations on data, enabling information manipulation, analysis, and transformation. In our proposed BCI, the detection unit, i.e., a fluorescence detector, is coupled by fiber optics. Fiber optics enable photon detection at the emission source close to the receptor protein, exposing a sensitive photodiode embedded in state-of-the-art cyber–physical systems for further processing.

5. Discussion and limitations

In the landscape of the IoBNT, BCIs occupy a central role, facilitating the convergence of biological and digital systems. Thereby, BCIs are the conduits through which biological data is seamlessly transduced into digital domains, e.g., enabling real-time monitoring, analysis, and control of living organisms and nanoscale devices, i.e., bio-nano things. The potential of BCIs is evident across various disciplines, including healthcare, environmental science, agriculture, and biomanufacturing. Nevertheless, as we traverse this novel terrain, it is imperative to acknowledge the multifaceted challenges and limitations that arise.

For our proposed BCI setup, limitations arise in the photon yield of the biological system due to the focus on observing single-molecule changes, i.e., the limit of detection could be reached in the single-molecule measurements. Therefore, photodiode detectors must be extremely sensitive, and fiber optics (or mirrors, as the case may be) must be highly efficient.

In the following, we distinguish between challenges in stability, fast responsiveness, and cyclicality, cf. Section 5.1, and ethical, societal, and regulatory considerations, cf. Section 5.2.

5.1. Stability, fast responsiveness, and cyclicality

Protein stability, temperature sensitivity, and limited longevity are common shortcomings of integrating biomolecules into machine circuits. While biological systems can replenish a used and damaged receptor by transcribing a gene into messenger RiboNucleic Acid (mRNA) and translating an mRNA to a functional protein, feasible technical solutions must address the continuous renewal of a BCI.

One caveat of our system is the instability of the purified GPCR at room temperature. One opportunity to face this issue is opened by artificial intelligence approaches and de novo protein design as revolutionized, e.g., by David Baker (Pillai et al., 2023). While an artificial GPCR has not been designed yet, creating a synthetic protein that combines all the best characteristics we desire, including a substantial increase in protein stability, would be imaginable.

Furthermore, current applications of BCIs are constrained by the need for precise volume control of agonist concentrations and pulsing frequencies to reliably activate the purified receptor. While this approach allows for specific and localized stimulation, it also introduces limitations regarding scalability and *in vivo* applicability. Future research should focus on developing adaptive, self-regulating systems adjusting dynamic agonist levels to real-time biofeedback, enhancing the stability and effectiveness of BCIs. Exploring novel biomaterials and microfluidic delivery systems such as microfluidic pipettes (Ainla et al., 2010, 2012; Ahemaiti et al., 2014) could enable finer control of the ligand accessibility allowing, for example, rapid stimulation patterns of varying frequency and/or ligand concentration.

Especially protein-based BCIs, while promising for molecular-to-optical communication, also face significant limitations when compared to alternative systems such as nanostructured materials designed for supercapacitor-based applications, e.g., in Waqas et al. (2024), Qayyum et al. (2023) and Shahzad et al. (2024). These alternatives often exhibit superior speed and stability due to their higher capacitance and enhanced cyclic stability, making them better suited for specific high-performance applications. In contrast, protein-based BCIs are inherently more prone to degradation, slower signal transmission, and less consistent performance under repeated use, which restricts their scalability and long-term viability.

5.2. Ethical, societal, and regulatory considerations

The ethical, societal, and regulatory dimensions for BCIs in the future IoBNT, encompassing data privacy, security, and responsible implementation, loom prominently. These concerns warrant sustained scholarly scrutiny and innovative solutions. The fusion of biological and cyber–physical systems, exemplified by BCIs, holds immense promises and underscores the imperative of meticulous exploration, ensuring that the ethical and societal ramifications are proactively addressed alongside technological advancements.

Ethical considerations focus on the moral principles guiding the development, deployment, and use of BCIs. For BCIs in the IoBNT context, ethical concerns include the following: *(i.)* Privacy: Ensuring that biological individuals can fully control their data collection, storage, and use, e.g., monitoring various parameters of the human body. *(ii.)* Control: Safeguarding against undue influence on individuals' health conditions, e.g., for drug release inside the human body, through BCI interfaces. *(iii.)* Non-maleficence: Avoid harm, especially considering the potential physical and psychological impacts on individuals using BCIs. Ethical considerations require that researchers prioritize the users' safety throughout the BCIs life cycle.

Societal considerations examine the impact of the BCI on the society. For BCIs, societal considerations address: *(i.)* Access: Ensuring fair access to the use of BCIs. *(ii.)* Trust: Building and maintaining public trust through transparency and accountability is essential to socially accepting IoBNT technologies.

Regulatory considerations involve legal frameworks, policies, and standards ensuring safe use of BCIs. For BCIs in the IoBNT ecosystem, regulatory concerns include the following: *(i.)* Data Protection: Setting policies for handling and securing sensitive biological data to protect against misuse. *(ii.)* Safety: Requiring comprehensive testing for the safety, efficacy, and long-term effects of BCIs on human health. Regulatory considerations aim to protect individuals by establishing guidelines that ensure the safe and transparent deployment of BCIs.

6. Conclusion and outlook

This work proposes a biocompatible BCI theoretical framework for transducing a biochemical into an electromagnetic signal utilizing the principle of GPCRs. In our proposed framework, a ligand binds to the extracellular portion of a GPCR, inducing a conformational change. The conformational change translates directly into the emission of photons, detectable by an optical sensor. We also discuss the limitations of the proposed BCI as well as ethical, societal, and regulatory considerations.

Future research involves setting up an experimental testbed to conduct initial trial runs of the proposed BCI. The system's components will undergo optimization, and potential applications, including personalized drug delivery and monitoring of the human cardiovascular system, will be explored. Additionally, we aim to develop mathematical models to characterize and quantify the capabilities of the proposed BCI.

CRediT authorship contribution statement

Pit Hofmann: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation. **Juan A. Cabrera:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Gunnar Schulte:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Frank H.P. Fitzek:** Writing – review & editing, Supervision, Resources, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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